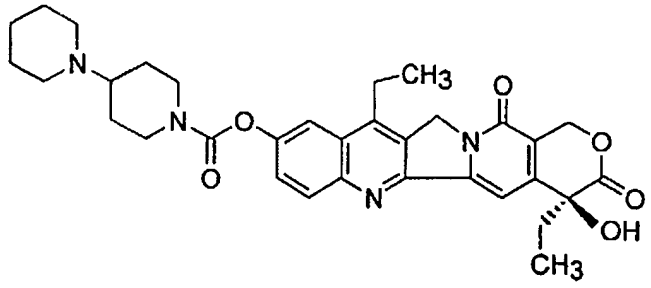
Method of Manufacturing of 7-Ethyl-10-[4-(1-piperidino)-1-piperidino]--carbonyloxycamptothecin

Field of the Invention

This invention relates to a method of manufacturing of 7-ethyl-10-[4-(1-piperidino)--1-piperidino]-carbonyloxycamptothecin of formula I

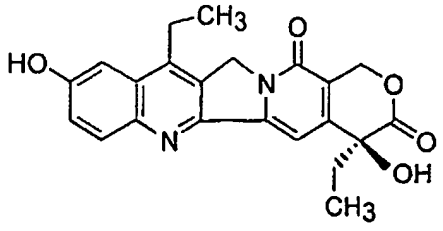


(I)

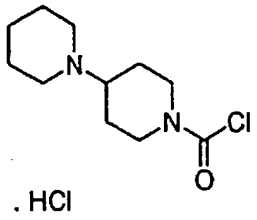
7-Ethyl-10-[4-(1-piperidino)-1-piperidino]-carbonyloxycamptothecin, which is also known as irinotecan base, is used for manufacturing of the cytostatically active irinotecan hydrochloride trihydrate, a topoisomerase inhibitor which is used in treatment of lung and rectum cancer.

Background of the Invention

7-Ethyl-10-[4-(1-piperidino)-1-piperidino]-carbonyloxycamptothecin has been hitherto prepared by condensation of 7-ethyl-10-hydroxycamptothecin of formula



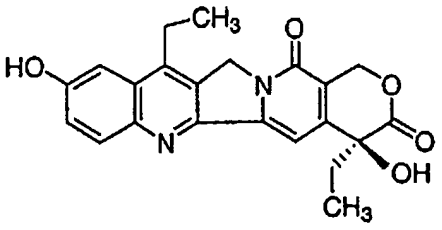
with 1-chlorocarbonyl-4-piperidinopiperidine hydrochloride of formula



in pyridine at room temperature. This method of preparation has been described in US 4 604 463. However, this method of preparation of irinotecan base suffers from the fact that in the condensation coloured impurities are formed which have to be removed by adsorption on a silica gel column and subsequent recrystallization from ethanol. These purification steps are accompanied by substantial losses of the final product and its yields are only about 64 %. Moreover, the method requires distillation of pyridine, extraction of a chloroform layer with sodium carbonate and sodium chloride solutions, and drying of the chloroform layer over magnesium sulfate. Therefore, a better method of preparation of irinotecan base was needed. Such a goal has been achieved by the method according to the present invention.

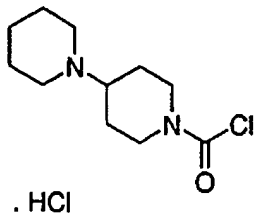
Summary of the Invention

The present invention relates to a method of manufacturing of 7-ethyl-10-[4-(1-piperidino)--1-piperidino]-carbonyloxycamptothecin of formula I, characterized in that 7-ethyl--10-hydroxycamptothecin of formula II



(II)

is condensed with 1-chlorocarbonyl-4-piperidinopiperidine hydrochloride of formula III



. HCl

(III)

in a polar aprotic solvent such as acetonitrile and in the presence of 4-dimethyl-aminopyridine. The condensation proceeds in suspension, where the polar aprotic solvent dissolves only 4-dimethylaminopyridine whereas 7-ethyl-10-hydroxycamptothecin and 1-chlorocarbonyl-4-piperidinopiperidine hydrochloride in this polar aprotic solvent remain undissolved. The amount of 1-chlorocarbonyl-4-piperidinopiperidine hydrochloride employed in the condensation reaction is preferably 1.3 to 3 mol, more preferably 1.6 to 1.9 mol, per 1 mol of 7-ethyl-10-hydroxycamptothecin. The amount of 4-dimethylaminopyridine used in the condensation ranges preferably between 1.5 and 4 mol, more preferably between 1.8 and 2.2 mol, per 1 mol of 7-ethyl-10-hydroxycamptothecin. The amount of the polar aprotic solvent used in the condensation is preferably 400 to 600 mol, more preferably 430 to 460 mol, per mol of 7-ethyl-10-hydroxycamptothecin. The condensation is performed preferably at a temperature from 70 to 80 °C, more preferably at 73 to 77 °C.

After end of the condensation, the present ballast compounds, consisting of e.g. 4-dimethyl-aminopyridine, 4-piperidinopiperidine and urea, are removed by washing of the obtained irinotecan base by a polar aprotic solvent, preferably acetonitrile. The yield of the condensation is at least 94 % and the obtained product contains at least 98 % of the desired irinotecan base, as determined by high-performance liquid chromatography.

The main advantage of the method according to this invention consists in that the work-up of the reaction mixture after condensation proceeds only with negligible losses of the final product and that the condensation is not accompanied with coloured impurities.

Examples

Example 1

Into a beaker in a sonication bath are placed 10 g (0.0247 mol) of 7-ethyl-10-hydroxy-camptothecin and 99 ml of acetonitrile. The obtained suspension is stirred in the sonication bath to homogeneity. Then the suspension is transferred quantitatively into a three-necked Keller flask equipped with a mechanical stirrer, thermometer and reflux condenser. Into the now empty beaker are now placed 6.2 g (0.0502 mol) of crystalline 4-dimethylaminopyridine and 40 ml of acetonitrile. The mixture is stirred until the crystalline portion dissolves. The obtained solution is then added quantitatively to the suspension of 7-ethyl-10-hydroxy-camptothecin. Into the empty beaker are then added 13.6 g (0.0434 mol) of 1-chlorocarbonyl--4-piperidinopiperidine hydrochloride and 79 ml of acetonitrile and the suspension is stirred in the sonication bath until homogeneous. The obtained suspension is transferred quantitatively into the three-necked Keller flask already containing 7-ethyl-10-hydroxycamptothecin and 4-dimethylaminopyridine in acetonitrile, and 382 ml of acetonitrile is added to the mixture. The obtained reaction suspension in the Keller flask is stirred at 75 °C for 5 h. After 2 h the lightly yellow suspension becomes thicker and its colour turns into a coffee-white one, indicating thus correct course of the reaction. After 5 h, the suspension is cooled to 18 to 20 °C, filtered and the filtration cake is washed with 300 ml of acetonitrile. After removing the acetonitrile by suction filtration, the obtained 7-ethyl--10-[4-(1-piperidino)-1-piperidino]-carbonyloxycamptothecin is dried at 60 to 65 °C to constant weight in a drier. This affords 14.1 g (yield 94.3 %) of product which, according to high-performance liquid chromatography, contains 98.9 % of 7-ethyl-10-[4-(1-piperidino)--1-piperidino]-carbonyloxycamptothecin.